heterologous gene to an animal heart *in vivo* by administering such a vector to the animal heart.

The Amendments to the Claims

Claims 1 and 20 have been amended to point out more particularly and claim more distinctly the present invention. Claims 21 and 22 have been added. The amendments to claims 1 and 20, as well as new claims 21 and 22, are supported by the specification at, for example, page 23, lines 13-23 (Example V). In Example V, the heterologous Neo expression cassette, comprising the SV40 promoter, SV40 splice site, DNA encoding the neomycin resistance gene, and SV40 polyadenylation elements, was inserted into the adenoviral backbone in the opposite orientation (i.e., 3' → 5' direction) relative to the CAT gene expression cassette (page 23, lines 19-23). It is clear from the Examples that the CAT gene expression cassette is inserted such that transcription occurs in the same direction as adenoviral E1 gene expression (i.e., 5' → 3' direction). For instance, in Examples I and III, the CMV promoter, the coding sequence for CAT, and globin poly(A) sites are inserted such that the order of genetic elements in the adenoviral backbone was nucleotides 0-353 of the adenoviral vector genome – CMV promoter – CAT gene – globin poly(A) (page 21, lines 14-29, page 22, lines 7-17, and Figure 2). Since the direction of transcription of the CAT gene is in the same orientation as adenoviral E1 gene transcription, the Neo expression cassette is inserted in the opposite orientation compared to the direction of transcription of the adenoviral region into which the cassette is inserted (i.e., the E1 region), thereby supporting the claim amendments of claims 1 and 20, as well as new claims 21 and 22, which depend from claim 1. As such, no new matter is added by way of these amendments. Separate documents setting forth the precise changes to the claims, as well as the text of all pending claims, as amended, are enclosed herewith.

The Pending Claims

Claims 1, 3, 4, 9, and 17-22 are pending. Claims 1, 3, 4, 9, 17, 21, and 22 are directed to an adenoviral vector. Claim 18 is directed to a host cell. Claim 19 is directed to a method of producing a selected protein. Claim 20 is directed to a method of administering a heterologous gene to an animal heart *in vivo*.

The Office Action

Claims 1, 3, 4, 9, and 17-20 have been rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. Claims 1, 3, 4, 9, and 17-20 have been rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Kirshenbaum et al. (*J. Clin. Invest., 92,*

381-389 (1993)), Quantin et al. (*Proc. Natl. Acad. Sci. USA, 89*, 2581-2584 (1992)), or Stratford-Perricaudet et al. (*J. Clin. Invest., 90*, 626-630 (1992)), in view of Huang et al. (*Nucl. Acid Res., 18*(4), 937-947 (1990)), Choi et al. (*Mol. Cell. Bio., 11*(6), 3070-3074 (1991)), Keating et al. (*Exp. Hematol., 18*, 99-102 (1990)), and International Patent Application WO 91/00747 (KabiGen). Reconsideration of this rejection is hereby requested.

Discussion of the Rejection under 35 U.S.C. §112, Second Paragraph

Claims 1, 3, 4, 9, and 17-20 have been rejected under Section 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, the Office Action alleges that the phrase "the direction of adenoviral gene transcription" lacks antecedent basis inasmuch as adenoviral gene transcription proceeds in both directions on a double-stranded adenoviral genome. The Office Action further contends that most insertion sites are palindromic restriction sites and, therefore, do not possess a particular orientation. Claims 1 and 20 have been amended to omit reference to the orientation of the insertion site. Claims 1 and 20 also have been amended to recite that the expression cassette is oriented such that the direction of transcription of an inserted heterologous gene is *opposite to the direction of transcription of the adenoviral region into which it is inserted.* As such, the pending claims are definite, and the Section 112 rejection should be withdrawn.

Discussion of the Rejection under 35 U.S.C. §103(a)

Claims 1, 3, 4, 9, and 17-20 have been rejected under Section 103(a) as allegedly being unpatentable over Kirshenbaum et al., Quantin et al., or Stratford-Perricaudet et al., in view of Huang et al., Choi et al., Keating et al., and KabiGen. This rejection is traversed for the reasons set forth below.

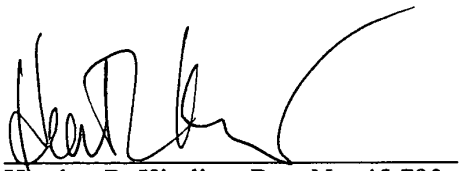
Claims 1 and 20 have been amended to more clearly describe the orientation of the expression cassette of the claimed adenoviral vector that comprises at least one insertion site for a heterologous gene. In particular, the expression cassette comprises a heterologous promoter positioned upstream from the insertion site, a eukaryotic splice acceptor and donor site positioned downstream of the promoter and upstream of the insertion site, and a polyadenylation sequence positioned downstream of the insertion site. The expression cassette is oriented such that the direction of transcription of an inserted heterologous gene is opposite to the direction of transcription of the adenoviral gene region into which the expression cassette is inserted. Positioning the expression cassette in the opposite direction of transcription of any adenoviral gene is not taught, or even suggested, by the references cited by the Office Action.

For example, the Kirshenbaum et al., Quantin et al., and Stratford-Perricaudet et al. references allegedly teach gene expression vectors comprising adenoviral sequences with various genetic elements, but not comprising a eukaryotic splice acceptor or splice donor site located between a heterologous promoter and a heterologous coding sequence. Huang et al. allegedly discloses the insertion of a splice site into a gene. Choi et al. allegedly discloses an increase in gene expression as a result of insertion of an intron between a promoter and a gene. Keating et al. allegedly discloses the use of the CMV promoter in expression cassettes. KabiGen allegedly discloses an expression vector with multiple cloning sites and a globin poly(A) site. Even if any or all of these references are combined, an adenoviral vector comprising an expression cassette oriented in the opposite direction of transcription -- relative to the adenoviral gene region into which the cassette is inserted -- does not result. None of the references teaches or suggests, alone or in combination, an adenoviral vector comprising an expression cassette that is oriented in a direction opposite to transcription of the adenoviral region into which it is inserted, much less the use of such an adenoviral vector to produce a selected protein or deliver a heterologous gene to an animal heart *in vivo*. The cited references furthermore provide no motivation for constructing such an adenoviral vector. Therefore, in that the cited references do not teach or suggest each and every limitation of the pending claims, the Section 103(a) rejection should be withdrawn.

Conclusion

The application is considered to be in good and proper form for allowance, and the Examiner is respectfully requested to pass this application to issue. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned agent.

Respectfully submitted,



Heather R. Kissling, Reg. No. 45,790
One of the Agents for the Applicant
LEYDIG, VOIT & MAYER, LTD.
Two Prudential Plaza, Suite 4900
180 North Stetson
Chicago, Illinois 60601-6780
(312) 616-5600 (telephone)
(312) 616-5700 (facsimile)

Date: May 15, 2002

CERTIFICATE OF MAILING

I hereby certify that this RESPONSE TO OFFICE ACTION (along with any documents referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, Washington, D.C. 20231.

Date: 5/15/02

RESPONSE UNDER 37 CFR 1.116
EXPEDITED PROCEDURE
EXAMINING GROUP 1600

PATENT
Attorney Docket No. 201895

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Falck-Pedersen

Application No. 08/653,114

Art Unit: 1632

Examiner: R. Schnizer

Filed: May 24, 1996

For: ADENOVIRUS GENE EXPRESSION SYSTEM

AMENDMENTS TO CLAIMS MADE IN RESPONSE TO OFFICE ACTION DATED MARCH 15, 2002

(additions indicated by underlining, deletions indicated by [brackets])

Amendments to existing claims:

1. (Four Times Amended) An adenoviral vector for expressing a heterologous gene(s) in a host cell, comprising at least one insertion site for cloning a selected heterologous gene, and, in an orientation opposite to the direction of [adenoviral gene transcription,] transcription of the adenoviral region into which it is inserted, [(a) at least one insertion site for cloning a selected heterologous gene; (b)] (a) a heterologous promoter positioned upstream from said at least one insertion site, wherein, upon cloning of the selected heterologous gene into said at least one insertion site, said gene is under the regulatory control of said heterologous promoter; [(c)] (b) a eukaryotic splice acceptor and splice donor site positioned downstream of said promoter and upstream of said at least one insertion site; and [(d)] (c) a polyadenylation sequence positioned downstream of said insertion site.

20. (Three Times Amended) A method of delivering a heterologous gene to an animal heart *in vivo*, wherein the method comprises administering to the animal heart an adenoviral vector comprising, in an orientation opposite to the direction of [adenoviral gene transcription,] transcription of the adenoviral region into which it is inserted, (a) a heterologous gene; (b) a promoter positioned upstream from the heterologous gene, the heterologous gene being under the regulatory control of the promoter; (c) a eukaryotic splice

acceptor and donor site positioned downstream of the promoter and upstream of the heterologous gene; and (d) a polyadenylation sequence.

21. (New) The adenoviral vector of claim 1, which comprises at least one insertion site for cloning a selected heterologous gene, and, in an orientation opposite to the direction of adenoviral E1 gene transcription, (a) a heterologous promoter positioned upstream from said at least one insertion site, wherein, upon cloning of the selected heterologous gene into said at least one insertion site, said gene is under the regulatory control of said heterologous promoter; (b) a eukaryotic splice acceptor and splice donor site positioned downstream of said promoter and upstream of said at least one insertion site; and (c) a polyadenylation sequence positioned downstream of said insertion site.

22. (New) The adenoviral vector of claim 1, which comprises at least one insertion site for cloning a selected heterologous gene, and, in an orientation 3' to 5' relative to adenoviral E1 gene transcription, (a) a heterologous promoter positioned upstream from said at least one insertion site, wherein, upon cloning of the selected heterologous gene into said at least one insertion site, said gene is under the regulatory control of said heterologous promoter; (b) a eukaryotic splice acceptor and splice donor site positioned downstream of said promoter and upstream of said at least one insertion site; and (c) a polyadenylation sequence positioned downstream of said insertion site.